**BCMAxCD3 bispecific antibody PF-06863135: preclinical rationale for therapeutic combinations**

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**Abstract**

**BCMAxCD3 bispecific antibody PF-06863135 is currently under evaluation in an ongoing Phase 3 clinical trial in relapsed/refractory (RR) multiple myeloma (MM) patients (NCT130269136). We showed previously that BCMAxCD3 bispecific has potent single agent activity in RR MM human bone marrow aspirates in vitro and in preclinical models of human myeloma (Grzeschik et al, MCT 2019). Herein, we used in vitro assays, ex vivo MM patient 3D cultures, and in vivo efficacy models to study therapeutic combinations of PF-06863135 with immune checkpoint inhibitors, immunomodulatory drugs (IMiD), and gamma secretase inhibitors (GSI).

**Introduction**

Uregulation of immune checkpoints, such as programmed cell death protein-1 (PD-1) or programmed death ligand 1 (PD-L1) has been demonstrated downstream of response to CD3 bispecifics. While PF-06863135 is effective as a single agent in ex vivo 3D primary MM cultures (EC50 0.2 mM), PD-L1 was upregulated on myeloma cells. We combined PF-06863135 with anti-PD-1 in subclinical and orthotopic myeloma models MM.1S and MM.15-PD-L1 in NSG mice engrafted with human T cells. PF-06863135 demonstrated single agent anti-tumor activity in the MM.1S models; however, in the MM.15-PD-L1 model, PF-06863135 activity was blunted. When given in combination with an anti-PD-1 blocking antibody, the full thrust of the single agent anti-tumor activity of PF-06863135 was restored.

**Results**

1. Dysfunctional, senescent like T cells may emerge downstream of T cell immunotherapies. IMiDs, such as lenalidomide, are a standard of care therapy in MM and result in immunomodulatory effects when combined with checkpoint inhibitors, IMiDs and GSI, supporting clinical rationale for dose escalation.

2. BCMA is shed from the surface of myeloma cells by gamma secretases, not only reducing cell surface BCMA-CD3 bispecific antibody PF-06863135: preclinical rationale for therapeutic combinations

3. BCMA is a T cell redirecting bispecific antibody against BCMA

4. BCMA is lineage specific target highly expressed in multiple myeloma

5. BCMA is a T cell redirecting bispecific antibody against BCMA

**Conclusions**

- We developed a potent BCMAxCD3 bispecific for the treatment of myeloma, including relapsed/refractory disease, and is promising in pre-clinical models.
- In preclinical studies, the anti-tumor efficacy of BCMAxCD3 at suboptimal doses is improved when combined with checkpoint inhibitors, IMiDs and GSI, supporting clinical rationale for dose expansion.
- Next-wave of BCMAxCD3 combinations may include GSI supported by preclinical evidence that BCMA is maintained on the myeloma cell surface.

**Acknowledgements**

- Pfizer CSI/legacy Rinat team in South San Francisco for preclinical development of PF-06863135
- Lui Zhang & Tae Tjin for providing GSI compound
- Frank Bendeit & LJ Pauwels for antibody GSI experiments

**Figure 1. BCMAxCD3 (PF-06863135) is a T cell redirecting full length bispecific antibody against BCMA**

**Figure 2. BCMAxCD3 is a potent & efficacious bispecific for myeloma – preclinical efficacy**

**Figure 3. BCMAxCD3 activity is enhanced by combination with lenalidomide in preclinical myeloma models**

**Figure 4. BCMAxCD3 activity is enhanced by combination with anti-PD1 in preclinical myeloma models**

**Figure 5. BCMAxCD3 activity is enhanced by combination with lenalidomide**

**Figure 6. Combinations with gamma secretase inhibitors may improve efficacy by reducing soluble BCMA & retaining BCMA on the cell surface**